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ORIGINAL ARTICLE

Heterogeneity of gestational diabetes (GDM) and challenges in developing a GDM risk score

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Abstract

Aims Gestational diabetes (GDM) affects a growing number of women and identification of individuals at risk, e.g., with risk prediction models, would be important. However, the performance of GDM risk scores has not been optimal. Here, we assess the impact of GDM heterogeneity on the performance of two top-rated GDM risk scores.

Methods This is a substudy of the RADIEL trial—a lifestyle intervention study including women at high GDM risk. We assessed the GDM risk score by Teede and that developed by Van Leeuwen in our high-risk cohort of 510 women. To investigate the heterogeneity of GDM, we further divided the women according to GDM history, BMI, and parity. With the goal of identifying novel predictors of GDM, we further analyzed 319 women with normal glucose tolerance in the first trimester.

Results Both risk scores underestimated GDM incidence in our high-risk cohort. Among women with a BMI ≥ 30 kg/m^2 and/or previous GDM, 49.4% developed GDM and 37.4% received the diagnosis already in the first trimester. Van Leeuwen score estimated a 19% probability of GDM and Teede succeeded in risk identification in 61%. The lowest performance of the risk scores was seen among the non-obese women. Fasting plasma glucose, HbA_{1c}, and family history of diabetes were predictors of GDM in the total study population. Analysis of subgroups did not provide any further information.

Conclusions Our findings suggest that the marked heterogeneity of GDM challenges the development of risk scores for detection of GDM.

Keywords Gestational diabetes · Pregnancy · Prediction of diabetes · Screening · Obesity · Heterogeneity

Introduction

The global epidemic of diabetes is leading to expanding health care costs as well as an increased burden for the affected individuals. Preventive measures are, therefore, essential. Lifestyle intervention trials have shown that type 2 diabetes [1, 2] and gestational diabetes (GDM) [3] can be prevented in high-risk groups, although the results have not been entirely consistent. Individualized interventions, however, are expensive, and therefore, a targeted intervention focusing on those at highest risk would be most feasible. To identify individuals at increased risk, the European Evidence-Based Medicine Guidelines (EBMG) [4] and the International Diabetes Federation [5] recommend using a risk score.

Risk scores can successfully identify individuals at increased risk for type 2 diabetes [6], and this has encouraged development of GDM risk scores as well. A recent review [7] validated 12 published GDM risk scores. The most common predictors were age, adiposity, ethnicity,

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family history of diabetes, history of GDM, and history of macrosomia. Score performance was, however, only moderate, and the authors requested more research before implementing GDM risk scores into practice.

Heterogeneity of type 2 diabetes is acknowledged [8, 9], but for GDM, it remains less well studied. We have previously shown that there is marked heterogeneity among GDM women [10]. Surprisingly, in the RADIEL study, the highest incidence of GDM was seen among non-obese women with a history of GDM; this despite showing no metabolic disturbances or diabetes-related autoantibodies during the first trimester. This might be suggestive of diverse pathophysiology. Some studies have identified subgroups of GDM women with various degrees of impairment in insulin secretion and sensitivity and presence of autoantibodies [11–13].

The aim of this study was to assess the heterogeneity of GDM and its influence on the moderate performance of GDM risk scores. We tested the two best-performing GDM risk scores from a recent review in the BMJ [7] in our high-risk cohort.

Methods

Study design

This is a secondary analysis of the RADIEL study (The Finnish GDM Prevention Study 2008–2014), conducted in the maternity hospitals of Helsinki (Helsinki University Hospital, HUH), and the South Karelia Central Hospital (SKCH) in Lappeenranta. The original study randomly assigned the participants into intervention and control groups, but in this study, they were combined as a cohort of women at high GDM risk. The RADIEL study has been described in detail previously [14].

Participants

Women at high GDM risk (BMI $\geq$ 30 kg/m^2 and/or previous GDM) entered the study voluntarily either in pre-pregnancy or in early pregnancy before 20 gestational weeks. The exclusion criteria included overt diabetes, multiple pregnancy, physical disability, substance abuse, severe psychiatric disorders, difficulties in co-operation, and medication influencing glucose metabolism. All participants provided written informed consent, and the Ethics Committees of HUH and SKCH approved the protocol. Participants with a normal oral glucose tolerance test (OGTT) in the first trimester served as the focus group when assessing GDM predictors.

To assess the heterogeneity of GDM we divided the women into four groups (A, B, C, D) according to their pre-pregnancy BMI, parity, and history of GDM, similar to our previous studies [10, 15]. Group A: obese primiparous women, group B: multiparous obese women without GDM history, group C: multiparous non-obese women with previous GDM, and group D: multiparous obese women with previous GDM.

Outcome and predictor assessment

The primary study outcome was GDM incidence. At enrollment (pre-pregnancy participants) as well as in the first (on average 13 gestational weeks) and in the second trimester (24–28 gestational weeks), all participants underwent a 75-g 2-h OGTT with diagnostic thresholds (at 0, 1, and 2 h) of 5.3–10.0–8.6 mmol/l. Predictor assessment included anthropometrics, medical history, and laboratory tests. In the beginning of the study, questionnaires covered family history of diabetes and cardiovascular diseases, regular medications, and chronic illnesses. History of macrosomia was self-reported, but hospital records provided verification for GDM history. Physical activity was self-reported as time per week spent in moderately strenuous activity. Food diaries and food frequency questionnaires provided data on dietary habits and were the base for calculating a dietary index, Healthy Food Intake Index (HFII), with higher scores indicating better adherence to the dietary recommendations [16].

Each visit included measurements of weight, waist, and hip circumference (non-pregnant participants), as well as blood pressure, measured from the right arm, in the sitting position, with a sphygmomanometer. Gestational weight gain (GWG) was the difference between pre-pregnancy weight (self-reported) and weight at the second trimester at 23.1 (median, IQR 22.4–24.1) gestational weeks. Glycated hemoglobin (HbA_{1C}), fasting plasma insulin (fP-insu), total cholesterol (fP-Kol), low-density lipoprotein (fP-LDL) and high-density lipoprotein (fP-HDL) cholesterol, and triglycerides (fP-trigly) from venous blood served as markers for lipid and glucose metabolism. Analysis additionally included adiponectin, interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), alanine aminotransferase (ALT), thyroid-stimulating hormone (TSH), and free thyroxine (fT4). HOMA-IR, estimating insulin resistance, was calculated by (FPI (mU/l) $\times$ FPG (mmol/l))/22.5, and HOMA-β, describing β-cell function, derived from formula (20 $\times$ FPI (mU/l))/(FPG (mmol/l) − 3.5). Our previous study provides information on the methods of laboratory analysis [10].

GDM risk calculations

To evaluate the performance of currently available and validated GDM risk scores in clinically distinct groups, we tested the risk calculations by van Leeuwen [17] and Teede [18]. These two risk scores showed the best performance according to a BMJ review [7]. The Van Leeuwen score

calculates the probability of GDM using simple clinical data as binary variables [17]. The formula used was probability of GDM = 1/[1 + exp(−β)], in which β is calculated as [−6.1 + (0.83 × non-Caucasian ethnicity) + (0.57 × family history of diabetes mellitus) − (0.67 × multipara without history of GDM) + (0.5 × multipara with history of GDM) + (0.13 × BMI)]. In the original study, 4% probability was the suggested cut-off point.

The risk score by Teede is based on giving points according to clinical characteristics: age (< 25 years 0 points, 25–34 years 1 point, and 35 years or older 2 points), BMI (< 29 kg/m^2 0 points, 30–34.9 kg/m^2 1 point, 35 kg/m^2 or more 2 points), ethnicity (Anglo-Australian, European or other 0 points, Polynesian, Maritime Southeast Asian, Chinese Asian, southern Asian or African 1 point, Mainland Southeast Asian 2 points), family history of diabetes (1 point), and history of GDM (2 points). A score of 4 or more was the suggested cut-off point [18].

Statistics

Mean and SD were calculated for continuous variables; frequency with percentages was calculated for categorical variables. Statistical comparison between groups was made by the analysis of variance (ANOVA), Chi-square test, or Fisher–Freeman–Halton test. In the case of violation of the assumptions (e.g., non-normality), a bootstrap-type ANOVA (5000 replications) was used. The bootstrap method is significantly helpful when the theoretical distribution of the test statistic is unknown or in the case of violation of the assumptions. Incidence of GDM was analyzed using generalizing estimating equation (GEE) models, and 95% confidence intervals with exact or maximum likelihood. Agreement, a measure of test reliability, was calculated by dividing the number of women who tested positive by the true number of women with the condition (GDM). All analyses were performed using STATA 14.1 (StataCorp LP, College Station,TX).

Results

In total, 510 women were included in the analysis. Among them, 88 women entered the study before pregnancy and the remaining in the first trimester. Total cumulative incidence of GDM was 49.4% (95% CI 45.0–53.8) and 37.4% (95% CI 33.2–41.8) of all participants were diagnosed in the first trimester. When compared to women without GDM, participants diagnosed with GDM were more often multiparous, had a history of GDM ($p < 0.001$), or a family history of diabetes ($p < 0.001$). There was no difference in pre-pregnancy BMI [no-GDM 31.7 kg/m^2 (95% CI 31.0–32.4) and GDM 31.6 kg/m^2 (95% CI 30.8–32.4) $p = 0.84$] or in first trimester characteristics such as dietary intake, physical activity, or age between women diagnosed with GDM compared with those not diagnosed.

In an attempt to characterize "early GDM"—women, we compared non-GDM women to women diagnosed either in the first or the second trimester. Women diagnosed in the first trimester had a higher pre-pregnancy BMI (mean

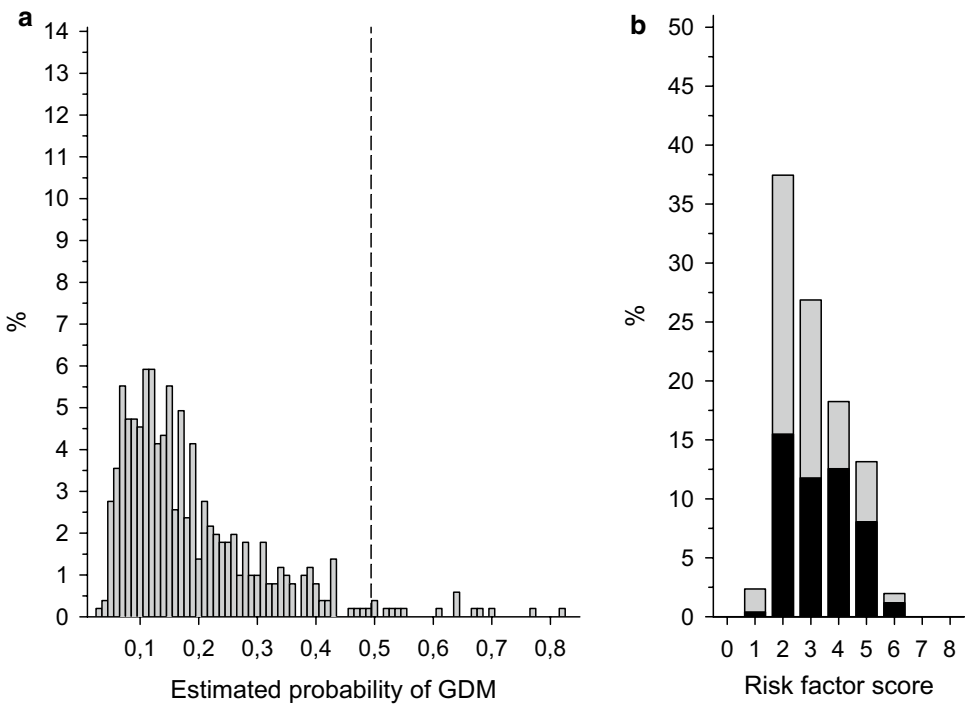

Fig. 1 **a** Histogram showing the distribution of estimated probability of GDM, calculated by the Van Leeuwen risk score. The real GDM incidence in RADIEL study is shown with dotted line. **b** Histogram showing the distribution of risk score points (grey) in the total study population, calculated by the Teede risk score. The black area within each risk score column indicates the presence of GDM among the RADIEL participants with that specific score

Table 1 Characteristics of the participants in the first trimester according to ABCD grouping

	A, $N=166$ Obese primiparous women	B, $N=97$ Obese multiparous women	C, $N=148$ Non-obese multiparous women, previous GDM	D, $N=99$ Obese multiparous women, previous GDM	p value
Age (years)	31 (5)	33 (5)	33 (4)	33 (5)	< 0.001
BMI (kg/m^2)	35.3 (4.2)	34.9 (3.6)	24.9 (2.6)	34.9 (4.2)	< 0.001
Educational attainment (years)	14.4 (2.1)	14.2 (1.9)	14.9 (2.0)	13.7 (2.0)	< 0.001
Family history of DM, *n* (%)	42 (25)	20 (22)	51 (35)	35 (37)	0.044
Gestational weeks, median (IQR)	13.0 (11.9, 14.4)	13.1 (12.3, 14.6)	12.9 (11.4, 14.0)	13.0 (11.7, 14.4)	0.10
Parity, *n* (%)					0.013
0	166 (100)	0 (0)	0 (0)	0 (0)	
1	–	67 (69)	88 (59)	52 (53)	
2	–	22 (23)	45 (30)	25 (25)	
3–	–	8 (8)	15 (10)	22 (22)	
Smoking, *n* (%)	9 (5)	5 (5)	4 (3)	4 (4)	0.66
Alcohol use, *n* (%)	6 (4)	4 (4)	9 (6)	8 (8)	0.40
Physical activity (min/week)	60 (30, 120)	60 (30, 120)	90 (30, 150)	60 (30, 125)	0.58
Diet (HFII)	9.5 (2.7)	9.6 (2.9)	10.8 (2.7)	10.1 (2.9)	< 0.001
Total triglycerides (mmol/l)	1.39 (0.54)	1.36 (0.51)	1.10 (0.37)	1.49 (0.81)	< 0.001
Fasting plasma glucose (mmol/l)	5.08 (0.44)	4.95 (0.34)	5.06 (0.41)	5.23 (0.40)	< 0.001
1 h—glucose (mmol/l)	7.32 (1.81)	7.07 (1.52)	7.72 (1.77)	7.93 (1.84)	< 0.001
2 h—glucose (mmol/l)	6.19 (1.31)	6.17 (1.18)	6.16 (1.40)	6.51 (1.52)	0.27
LDL cholesterol (mmol/l)	2.72 (0.60)	2.91 (0.81)	2.65 (0.70)	2.86 (0.71)	0.025
Fasting plasma insulin (mU/l)	11.13 (8.14)	9.28 (3.78)	5.75 (3.63)	9.83 (5.21)	< 0.001
Total cholesterol (mmol/l)	4.78 (0.72)	5.02 (0.92)	4.74 (0.84)	5.01 (0.92)	0.017
hs-CRP (mmol/l)	9.55 (7.18)	8.53 (5.99)	4.29 (3.78)	11.18 (11.35)	< 0.001
Adiponectin (mg/ml)	15.8 (6.1)	16.2 (5.3)	18.3 (6.5)	15.2 (5.5)	0.004
HbA_{1c} (%)	5.24 (0.30)	5.27 (0.31)	5.25 (0.28)	5.33 (0.35)	0.18
TNF-alfa (pg/ml)	11.5 (8.9)	10.9 (5.6)	12.1 (9.5)	10.8 (5.1)	0.56
IL-6 (pg/ml)	6.18 (6.80)	5.07 (5.45)	9.27 (14.40)	5.20 (3.40)	0.020

Values are presented as means (SD) unless otherwise indicated

32.4 kg/m^2) both compared with those diagnosed in the second trimester (28.9 kg/m^2) and the non-GDM group (31.7 kg/m^2 $p<0.001$). There was also a trend towards a difference in family history of diabetes (no-GDM 21%, early GDM 41% and standard GDM 28%, $p=0.069$).

We tested two selected GDM risk scores in our high-risk cohort. Figure 1a, b illustrates their performance. Estimated mean probability of GDM calculated by van Leeuwen score was 19%, which was lower than the real GDM incidence 49%. The risk score by Teede succeeded in risk identification in 61% of cases, with numerous GDM women falling below the 4 points' cut-off limit.

We then divided the high-risk women into groups (A, B, C, D) according to their BMI, parity, and history of GDM. Table 1 shows the first trimester characteristics of these groups, whereas Fig. 2 presents the cumulative GDM incidence. When compared to other groups, the non-obese women with previous GDM (group C) showed significantly better metabolic characteristics in the first trimester. Compared to group A, the risk of GDM was similar in group B [OR 0.87 (95% CI 0.51–1.48)] and markedly higher in group C [OR 2.52 (95% CI 1.60–3.97)] and group D [OR 4.96 (95% CI 2.87–8.58)], who both had a history of previous GDM.

The Van Leeuwen risk score was tested also separately in groups A, B, C, and D (Fig. 3). Groups A and D had the highest estimated probability of GDM (mean 21% and 31%, respectively), and in groups B and C, it was lower (mean

11%). Figure 4 shows risk scores by Teede in the ABCD groups together with the true incidence of GDM. Teede score was most successful in risk identification in group B (69% agreement) and worst in the non-obese group C (52% agreement).

Due to the weak performance of the previous scores, we further investigated this high-risk group to find useful risk markers taking simultaneously into account the heterogeneity of GDM. Among the 319 participants with normal glucose tolerance in the first trimester, we analyzed the most commonly used risk markers (age, family history of diabetes, fasting glucose, HbA_{1c}, lipids, and hs-CRP) in the total study population and inside the ABCD groups by multiple logistic regression model. The supplementary table presents the results concerning the total study population. In group A, first trimester fasting plasma glucose was associated with GDM risk [OR 3.76 (95%CI 1.48–9.53) $p = 0.005$], but this was not seen in the other groups. None of the markers showed predictive potential in groups B, C, or D. In predicting GDM, there was no interaction between family history of diabetes ($p = 0.76$) or diet (HFII) ($p = 0.70$) and allocation to ABCD group.

Discussion

The best-rated GDM risk scores seem to underestimate the incidence of GDM in high-risk women, even when tested in phenotypically distinct groups. Our results demonstrate a considerably high incidence of GDM already in the first trimester: within this high-risk group with a BMI ≥ 30 kg/m^2 and/or previous GDM, almost half (49%) developed GDM and 37% received the diagnosis already in the first trimester. In the subgroup of primiparous obese women, fasting glucose was a predictor of GDM, but in the other subgroups, there were no identifiable markers. Notably, women with previous GDM are at increased risk of GDM already at the first trimester; 38% of the non-obese and 63% of the obese women with previous GDM received an "early GDM" diagnosis. This challenges the development of GDM risk scores even further.

There is ongoing debate on the appropriate GDM screening strategy. Following the HAPO study [19], The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) published new diagnostic thresholds for GDM and in 2013 also WHO endorsed them [20] recommending universal screening at 24–28 weeks. EBCOG (European Board and College of Obstetrics and Gynaecology) has raised concern about a universal screening strategy in Europe [21], where procedures vary highly. The diagnostic thresholds and the importance of first trimester screening are even more controversial. IADPSG recommends [22] a fasting glucose cutoff of 5.1 mmol/l and directing the early screening towards high-risk women (overweight/obesity, previous GDM, family history of diabetes, previous macrosomia, or polycystic ovary syndrome (PCOS), and certain ethnicities). Our results support the IADPSG recommendation, since with fasting glucose 5.3 mmol/l as a cutoff, among women with either previous GDM or obesity, the first trimester incidence of GDM was 37.4%.

One obstacle for universal OGTT screening is naturally financial. Furthermore, it is time-consuming and burdensome requiring overnight fasting. Studies have, therefore, aimed at finding predictors of GDM to enable risk-factor-based screening. BMI has been considered the main risk factor for GDM, but a recent study showed that a random plasma glucose performed better than age or BMI in early pregnancy [23]. Still, with a ≥ 7.5 mmol/l plasma glucose cutoff, the sensitivity was only 0.70 and specificity 0.90. Results concerning HbA_{1c} and adiponectin [24–26] have not been convincing either. In a retrospective study, the second trimester HbA_{1c} was strongly associated with perinatal outcomes, but it was not useful in first trimester screening [25] and a prospective study [24] found an association only between first trimester HbA_{1c} and macrosomia.

One approach for identifying women at GDM risk has been the development of prognostic models, taking advantage of commonly available clinical data. A systematic review in the BMJ [7] validated 12 GDM risk scores. Age, BMI, ethnicity, family history of diabetes, history of GDM, and history of macrosomia were the most common predictors. All prognostic models were evaluated in a Dutch

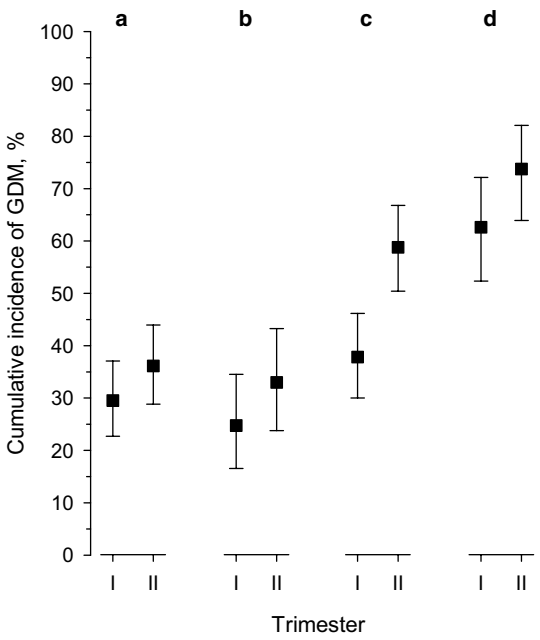

Fig. 2 Cumulative incidence of GDM in the first and second trimester according to ABCD groups

cohort of 3723 women, where only women with risk factors or symptoms of GDM underwent an OGTT, based on WHO 1999 diagnostic guidelines (fasting glucose 7.0 mmol/l and 2-h glucose 7.8 mmol/l). The C-statistics ranged from 0.67 to 0.77, and even the best models, Teede (0.77) [18] and Van Leeuwen (0.74) [17], performed only moderately. In accordance with our findings, they also demonstrated differences in the score performance based on parity [7]. In our study cohort, these risk scores underestimated the probability of GDM, but especially among the non-obese women with previous GDM (11% versus 59%). This highlights the difficulty of finding normal-weight women at high GDM risk.

Most recent studies have also applied more advanced methods for risk identification [27–29]. For example, the prediction model derived from the UPBEAT study [29] combined clinical data with HbA_{1c}, glucose, fructosamine, triglycerides, adiponectin, and sex hormone-binding globulin (SHBG). This prognostic model for obese women had a C-statistic of 0.77 and 50% of score-positive women developed GDM. This is similar to our results; using BMI ≥ 30 kg/m^2 or previous GDM as risk factors, we identified a group with a similar diagnosis rate. In addition, we analyzed other markers including inflammatory markers, HOMA-IR, and HOMA-ß, but in these subgroups, they were not successful in predicting GDM.

Several studies have focused on the heterogeneity of type 2 diabetes [8, 9] and current practice is tailoring the treatment according to the underlying pathophysiology [30]. Although the first studies describing GDM heterogeneity date from the 1980s [12, 13], there is still insufficient

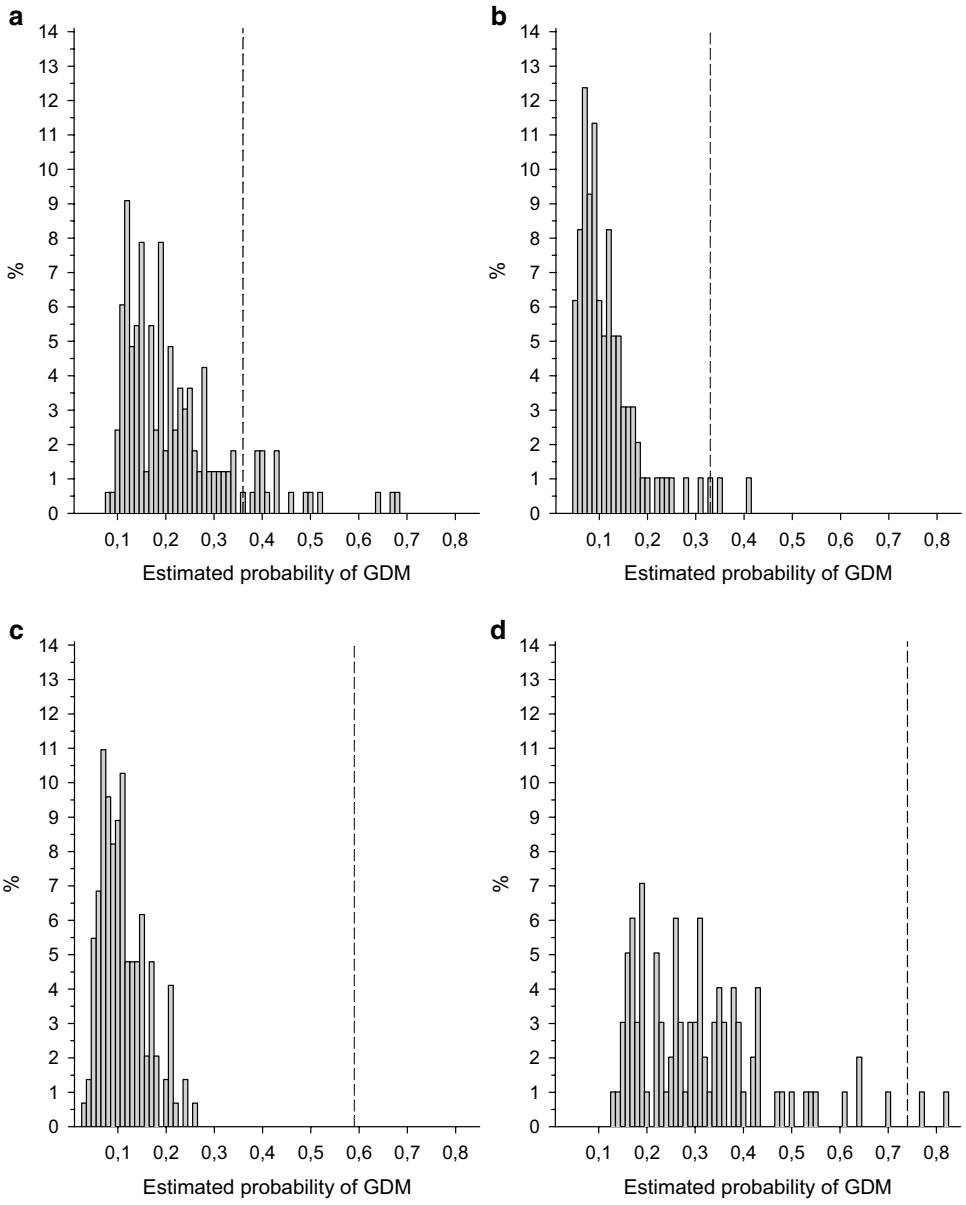

Fig. 3 Histogram showing the distribution of estimated probability of GDM, calculated by the Van Leeuwen risk score, separately in ABCD groups. The real GDM incidence in the RADIEL study is shown with dotted line

knowledge on varying backgrounds. Damm [12] demonstrated that obese and non-obese GDM women have distinct insulin secretion profiles; the non-obese had a lower and slower insulin response profile which persisted even 5–11 year postpartum. According to a recent study, 51% of GDM women had primarily a deficiency in insulin sensitivity, 30% in insulin secretion, and 18% a mixed pathophysiology [31]. Elevated cesarean section and macrosomia rates were associated only with insulin resistance highlighting the importance of the underlying pathophysiology.

We divided the participants of the RADIEL study [14] into four groups according to BMI, parity, and GDM history. Although the non-obese women had better metabolic health and diet scores in early pregnancy, their GDM incidence was markedly higher in the second trimester [10]. The previous studies have shown a higher occurrence of diabetes-related autoantibodies among non-obese women [11], but in the RADIEL study, the overall prevalence of autoimmunity was low and did not provide an explanation. Together with the previous studies, our findings emphasize the marked heterogeneity of GDM and elucidate the varying risk profiles according to parity and BMI. In this high-risk cohort, the potential risk predictors were fasting glucose, HbA1c, and family history of diabetes; unfortunately, we failed in finding tools for identifying the non-obese women at high risk.

Strengths of our study are the inclusion of non-obese women and measurements of numerous biomarkers. In addition, in contrast to many other studies, OGTT was performed also in the first trimester, and therefore, we have detailed information on the glycemic status throughout pregnancy. Our population was ethnically homogenous, Caucasian, which affects our findings as both scores tested emphasize ethnicity, and this also limits the generalizability of our findings. Lack of a control group from the normal population or non-obese women without previous GDM can be considered a weakness. The diagnostic strategy and the OGTT thresholds were different in our study compared to those used in the development of the current risk scores, which might influence our findings. Our diagnostic thresholds, however, exceed the current IADPSG recommendations and, therefore, fail in finding all women currently defined to have GDM. Test performance was evaluated by calculating agreement between the tests, but it should be acknowledged that it does not determine performance of the test on an individual level. We also recognize the challenges, when testing a risk score developed for the general population in a high-risk population. Our aim was, however, to investigate the impact of GDM heterogeneity on the performance of GDM risk scores. In addition, as these risk calculations give an individual risk estimate, i.e., a probability of a disease based on individual characteristics not depending on the surrounding population, this provides a possibility to assess the performance of the risk scores also in a high-risk cohort.

In conclusion, we hypothesize that the underlying heterogeneity offers an explanation for the difficulties in creating a GDM risk score. It might be impossible to create a universal risk score, but if resources are low and targeting the diagnostic tests or preventive measures is needed, our simple model using BMI and GDM history detects a risk group with a 50% diagnosis rate, a similar performance to the previous much more complex models. Based on our results, we hypothesize that universal screening, in accordance with WHO and IADPSG guidelines, could be the only way to identify non-obese women at high GDM risk in their first pregnancy. In the age of personalized medicine [32], the heterogeneous background of GDM requires more research for better understanding of the pathophysiology, possible

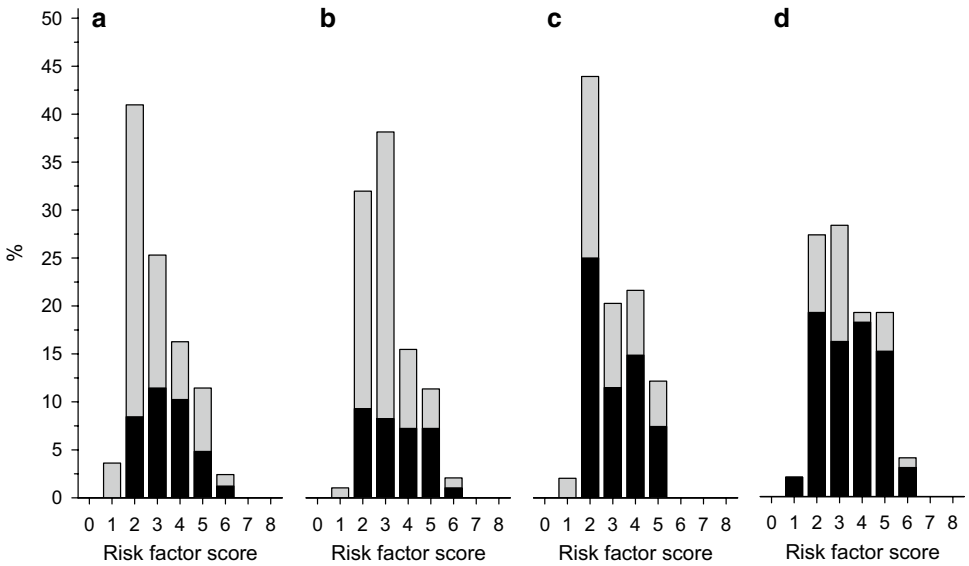

Fig. 4 Histogram showing the distribution of risk score points (grey), calculated by the Teede risk score, separately in ABCD groups. The black area within each risk score column indicates the presence of GDM among the RADIEL participants with that specific score

methods of treatment, and consequences for the mother and child in the future.

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Author contributions EH participated in the implementation of the study, literature search, data interpretation, and the drafting and editing of the article. JGE is the principal investigator of the study, and participated in the implementation of the study, and advised on editing the article. AT participated in the design of the study and helped with the drafting and editing of the article. BS-L participated in the design of the study, coordinated the study in Lappeenranta, and helped with the statistical analyses and drafting of the article. SBK initiated, participated in the design of, and coordinated the study; and helped in the drafting and editing of the article. All authors have read and approved the final version of the manuscript. EH is the guarantor of this work and, as such, had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest associated with this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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